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Epidemiology of alcohol-associated cancers

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Abstract

Alcohol, especially in combination with smoking, is a well-established risk factor for cancers of the oral cavity and pharynx, esophagus, and larynx, with 25% to 80% of these cancers being attributable to alcohol. Rates of these cancers in the United States have been decreasing in recent years, possibly because of reductions in cigarette smoking and alcohol use. Chronic alcohol consumption has been linked with increased risk of liver cancer in epidemiologic studies. However, the rising rates of this cancer in the United States are most likely due to the increasing prevalence of chronic hepatitis B and C infections. Epidemiologic evidence has linked light to moderate intake of alcohol to cancers of the colorectum and female breast. These cancers are common in developed countries, so even small increases in risk can have important public health implications. Although results of most epidemiologic studies have provided little or no support for a causal relation between light and moderate alcohol use and risk of pancreatic cancer, a possible role of heavy alcohol consumption cannot be ruled out. Further studies of these cancers are needed to clarify the role of type of alcoholic beverage, the role of alcohol concentration, and the dose-response curve at low concentrations of alcohol. Future research also should be designed to promote the use of uniform ways to report alcohol intake and uniform measures for analysis, to include the investigation of alcohol-associated cancer risks in U.S. minority populations, to enhance experimental work to better understand the underlying mechanisms through which alcohol promotes carcinogenesis, and to develop preventive strategies.

Keywords: Alcohol; Breast cancer; Cancer; Colorectal cancer; Esophageal cancer; Laryngeal cancer; Oral cancer; Pancreatic cancer; Pharyngeal cancer; Tobacco; Trends

1. Introduction

This article provides an overview of the epidemiology of seven alcohol-associated cancers (oral cavity and pharynx, squamous cell carcinoma of the esophagus, larynx, liver, colorectum, breast, and pancreas) and a review of methodologic issues related to the quality of the alcohol data obtained from epidemiologic studies. U.S. incidence trends for these alcohol-associated cancers as well as U.S. patterns of drinking and smoking are also examined. Alcohol-related risks are presented from recent meta-analyses for all seven cancer sites and from National Cancer Institute (NCI) studies for cancers of the oral cavity and pharynx, squamous cell carcinoma of the esophagus, and pancreas. This article concludes with a discussion of future research directions.

2. Methods and methodologic issues

Issues related to collection of alcohol data in epidemiologic studies include difficulties in quantifying prior long-term alcohol intake (Schottenfeld, 1979). Alcohol data are generally obtained from structured questionnaires or interviews, but self-reports often underestimate true consumption. Conversely, case-control and cohort studies are used to assess usual past intake of alcoholic beverages, which may overestimate true consumption (Collaborative Group on Hormonal Factors in Breast Cancer, 2002). Measurement error is also likely to occur with summarization across different types of alcoholic beverages. Although there is great interest, it has been difficult to assess risk for different types of alcoholic beverages and to quantify risk for low levels of alcohol intake (Fraumeni, 1979). There is also a void in the U.S. literature with little data available on alcohol-associated risks in U.S. minorities, especially Asian Americans, Hispanics and Latinos, and American Indians and Alaskan Natives.

Incidence data for the seven alcohol-associated cancer sites were obtained from nine Surveillance, Epidemiology,

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and End Results (SEER) registries (Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco–Oakland, Seattle–Puget Sound, and Utah) that cover approximately 10% of the U.S. population [Surveillance, Epidemiology, and End Results (SEER) Program, 2004]. The SEER*Stat statistical software package was used to calculate age-adjusted (to the 2000 U.S. standard population) incidence rates by race, sex, and time period of diagnosis (1973-1975, 1976-1980, 1981-1985, 1986-1990, 1991-1995, 1996-2000) (Surveillance Research Program, 2004). Figures were prepared by using the ratio of 1 log cycle to 40 years = 1, so that a slope of 10 degrees represents an annual change of 1% (Devesa et al., 1995).

On the basis of a review of the epidemiologic literature from 1966 through 2000, data were obtained from a meta-analysis of alcohol drinking and cancer risk. With the application of meta-regression models, those data provided pooled alcohol-related relative risks for men and women combined in comparison with those of nondrinkers for all alcohol-associated cancers except breast cancer (Bagnardi et al., 2001). The meta-analysis published in 2001 included 235 studies with more than 117,000 subjects. The number of studies per alcohol-associated cancer site ranged from 17 for pancreas to 28 for esophagus.

Alcohol-related relative risks for female breast cancer were obtained from a meta-analysis of drinking, smoking, and breast cancer risk published in 2002 (Collaborative Group on Hormonal Factors in Breast Cancer, 2002). The meta-analysis included 53 studies with more than 58,500 cases and 95,000 control subjects. Grams of alcohol consumed was estimated by assuming that one drink contained approximately 12 g of alcohol.

3. Results

Alcohol is a strong risk factor for upper aerodigestive tract (UADT) cancers of the oral cavity and pharynx, esophagus, and larynx (Jensen et al., 1996). The earliest report was by a Boston surgeon, J. C. Warren, who, in 1836, described a case of tongue cancer in a tobacco chewer with a ''predisposition'' owing to chronic use of spirits (Warren, 1837). The earliest reported ''association'' was an excess of esophageal cancer among alcoholics in Paris in 1910 (Lamu, 1910). On the basis of findings of various studies, 25% to 80% of UADT cancers are attributable to alcohol (Brown et al., 2001; Franceschi et al., 1990). Smoking is also a strong risk factor for these cancers, with heavy smokers and heavy drinkers at greatest risk for a UADT cancer.

On the basis of data obtained from the National Institute on Alcohol Abuse and Alcoholism (NIAAA), per capita alcohol consumption peaked in the United States in 1980 to 1981 at 2.76 gallons and declined 21% to 2.18 gallons in 2000 (Nephew et al., 2003) because of lower rates of heavy drinking among whites and higher rates of abstinence among blacks and Hispanics (Caetano & Clark, 1998). Recent declines in UADT cancers have ''mirrored'' decreases in liquor consumption, which peaked in 1969 at 1.13 gallons per capita and has declined 42.5% during the past several decades to 0.65 gallons per capita in 2000. Changes in beer and wine consumption have been less dramatic and less consistent. Per capita beer consumption declined 12.2% from a high of 1.39 gallons in 1981 to 1.22 gallons in 2000, whereas per capita wine consumption declined 20.5% between 1986 (0.39 gallons) and 2000 (0.31 gallons) (Nephew et al., 2003). In comparison with blacks, a higher percentage of whites drink, and, in comparison with females, a higher percentage of males drink. However, a decrease in alcohol use has been observed for all race–sex groups in recent years (Caetano & Clark, 1998). The percentage of adults aged 18 years and older who are current smokers declined 46% between 1965 and 2001, but the smoking prevalence has remained consistently higher among black men than among white men and among men than among women (Freid et al., 2003). It is likely that changes in smoking and drinking habits explain, in part, the overall decline in UADT cancers.

Incidence trends for oral and pharyngeal cancer are displayed in Fig. 1. Incidence rates in black men show a peak of 28.0/100,000 in the time period 1986 through 1990 and a downward trend in recent years to a rate of 21.3/100,000 during 1996 through 2000. There was a consistent decrease in incidence for white men from 21.1/100,000 in the time period 1973 through 1975 to 16.3/100,000 in 1996 through 2000. Rates for females are two to three times lower than those for males (range, 6.1/100,000–8.7/100,000), and rates also show a downward trend in recent years. Pooled oral cancer risks associated with grams of alcohol consumed per day ranged from 1.75 [95% confidence interval (CI) = 1.70-1.82] for 25 g (about two drinks) to 2.85 (95% CI = 2.70-3.04) for 50 g (about four drinks) to 6.01 (95% CI = 5.46-6.62) for 100 g (about eight drinks) (Bagnardi et al., 2001).

A population-based case-control study was conducted at the NCI to determine reasons for the high rates of oral and pharyngeal cancer in Puerto Rican natives in comparison with the rates in mainland Hispanics. The 535 cases and 1,031 control subjects were Puerto Rican men and women, aged 21 to 79 years. Alcohol and tobacco were found to be strong independent risk factors for oral cancer in Puerto Rico, with a multiplicative effect from combined exposures. In comparison with findings for nondrinkers, a significant dose-response trend with number of drinks of alcohol consumed was observed for men ($P < .001$), reaching 7.7 (95% CI = 3.3-17.9) for 43 or more drinks per week. An elevated odds ratio (OR) of 9.1 (95% CI = 0.9-94.2) was observed for the small number of women who drank 22 or more drinks per week (Hayes et al., 1999). Results of this study also showed that heavy drinkers (>57 drinks per week) homozygous for the fast-metabolizing alcohol dehydrogenase type 3^1 allele ($ADH3^{1\text{-}1}$) had

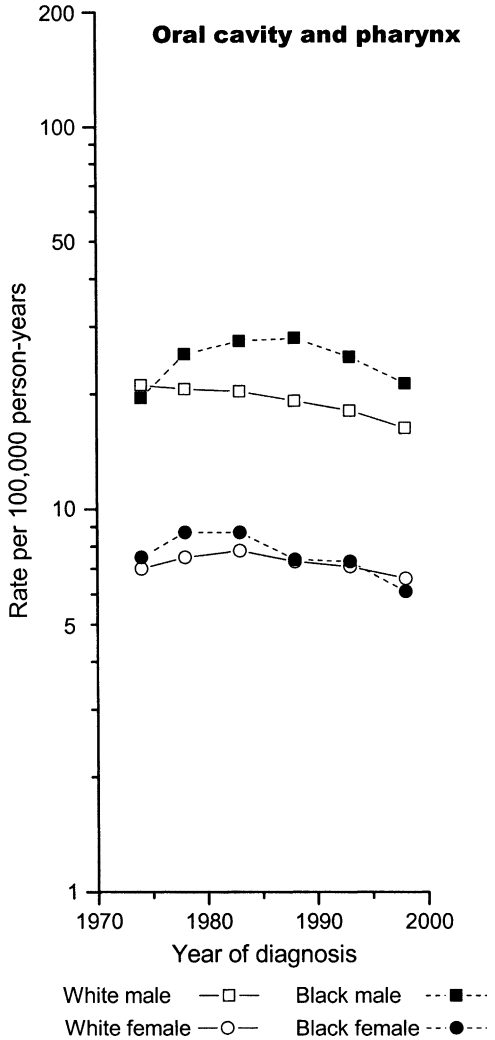

Fig. 1. Age-adjusted (2000 U.S. standard) incidence rates for cancer of the oral cavity and pharynx by race and sex, in nine SEER registries, 1973-2000. From Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence – SEER 9 Regs Public-Use, Nov 2003 Sub (1973-2001), National Canter Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2004, based on the November 2003 submission.

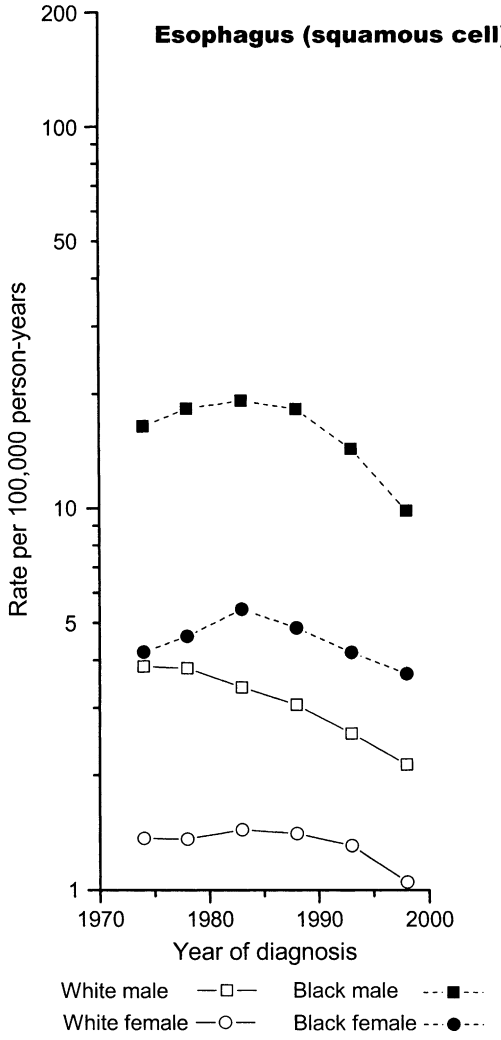

Fig. 2. Age-adjusted (2000 U.S. standard) incidence rates for squamous cell carcinoma of the esophagus by race and sex, in nine SEER registries, 1973-2000. From Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence – SEER 9 Regs Public-Use, Nov 2003 Sub (1973-2001), National Canter Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2004, based on the November 2003 submission.

substantially increased risks of alcohol-related oral cancer (OR = 40.1, 95% CI = 5.4-296.0) in comparison with the risks of nondrinkers with the *ADH3*$^{1-1}$ genotype (Harty et al., 1997).

The downward trends in squamous cell carcinoma of the esophagus (Fig. 2) are evident for all race–sex groups. There was a striking 48.4% decrease in incidence rates for black men during the past two decades, from a high of 19.2/100,000 in the time period 1981 through 1985 to a low of 9.9/100,000 in 1996 through 2000. Rates in black women also peaked in the time period 1981 through 1985 at 5.4/100,000 before dropping 30.2% to 3.7/100,000 in the most recent time period. White men exhibited a dramatic 45.9% drop in incidence from 3.9/100,000 in the time period 1973 through 1975 to 2.1/100,000 in 1996 through 2000. Rates for white females declined to 1.1/100,000 in the most recent time period. The pooled risks for esophageal cancer ranged from 1.51 (95% CI = 1.48-1.55) for 25 g of alcohol consumed per day to 2.21 (95% CI = 2.11-2.31) for 50 g of alcohol consumed per day to 4.23 (95% CI = 3.91-4.59) for 100 g of alcohol consumed per day (Bagnardi et al., 2001). Pooled risks for esophageal cancer are lower than the pooled risks for oral cancer and may reflect the inclusion in the meta-analysis of both squamous cell carcinoma of the esophagus and adenocarcinoma of the esophagus, a major histologic type of esophageal cancer that is not strongly related to alcohol intake (Enzinger & Mayer, 2003).

A population-based case-control study of squamous cell carcinoma of the esophagus was conducted by the NCI in Atlanta, Detroit, and New Jersey to investigate reasons for

the large black–white difference in incidence rates. At the time of the study, rates of squamous cell carcinoma of the esophagus were five times higher for blacks than for whites in the three study areas combined: 19.4/100,000 versus 3.6/100,000. In this study, there were 373 male cases (124 white, 249 black) and 1,364 male control subjects (750 white, 614 black) aged 30 to 79 years. Striking dose-response trends ($P < .001$) were seen for both white and black males, but the ORs were higher for blacks at each level of consumption. Risks reached 26.9 (95% CI = 11.9-60.9) for black consumers and 16.1 (95% CI = 6.7-38.9) for white consumers of 85 or more drinks per week in comparison with findings for nondrinkers or light drinkers of seven or fewer drinks per week. In addition, higher risks were observed at each alcohol intake level for white and black men who were heavy smokers in comparison with those who were light smokers (Brown et al., 1994). It was estimated that moderate-to-high levels of drinking (more than eight drinks per week) and use of any tobacco product accounted for 92% of the black excess in incidence rates in this population (Brown et al., 2001).

On the basis of SEER data, larynx cancer incidence rates among black men peaked at 15.5/100,000 in the time period 1986 through 1990 and have exhibited a downward trend in the last two time periods, reaching 12.1/100,000 in 1996 through 2000 (Fig. 3). Rates for white men have shown a fairly consistent downward trend from 9.9/100,000 in the time period 1976 through 1980 to 7.1/100,000 in 1996 through 2000. Trends in women are less consistent and rates are much lower, ranging from 2.3/100,000 to 3.1/100,000 for blacks and 1.5/100,000 to 1.8/100,000 for whites. The pooled alcohol-related risks for larynx cancer ranged from 1.38 (95% CI = 1.32-1.45) for 25 g per day to 1.94 (95% CI = 1.78-2.11) for 50 g per day to 3.95 (95% CI = 3.43-4.57) for 100 g per day (Bagnardi et al., 2001).

There has been much speculation in the UADT cancer literature as to whether the alcohol-associated risk is due to any type of alcohol or if certain types of alcoholic beverage convey different risks. Through a number of studies in the United States and elsewhere, higher risks for certain types of beverages have been identified. However, the type of high-risk beverage differs in different populations and may be a combination of the most popular type used in an area and the culturally or economically determined drinking habits of the population (Franceschi et al., 1990; Jensen et al., 1996). Findings of studies conducted in Italy and Switzerland have supported the suggestion that, at any level of intake, subjects who drank alcohol outside meals (i.e., not with food) were at greater risk of UADT cancers than subjects who drank only with meals, possibly because of the more rapid absorption of alcohol (Dal Maso et al., 2002). Results of several studies seem to have indicated that concentrated liquor is associated with higher risk than diluted liquor because of local effects on tissue (Brown et al., 1997; Huang et al., 2003). In the NCI squamous cell carcinoma of the esophagus study, the adjusted ORs for men who drank liquor straight in comparison with those who drank liquor diluted with water or another type of mixer were 1.7 (95% CI = 0.9-3.1) and 1.6 (95% CI = 1.0-2.5) for white and black men, respectively (Brown et al., 1997). In the NCI Puerto Rican study, the risk was substantially greater for those who drank liquor straight versus diluted (OR = 4.0, 95% CI = 2.4-6.7), with the greatest risk observed among heavy smokers who drank liquor straight (Huang et al., 2003).

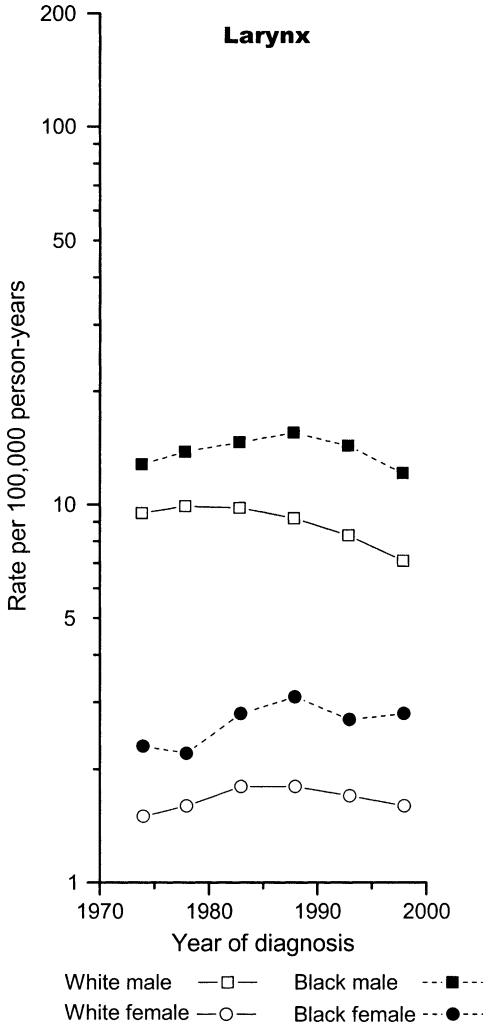

Fig. 3. Age-adjusted (2000 U.S. standard) incidence rates for laryngeal cancer by race and sex, in nine SEER registries, 1973-2000. From Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence – SEER 9 Regs Public-Use, Nov 2003 Sub (1973-2001), National Canter Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2004, based on the November 2003 submission.

Cancers of the liver, colorectum, and breast are less strongly related to alcohol use than are the UADT cancers. Primary liver cancer has been associated with chronic use of alcohol in a number of epidemiologic studies (Jensen et al., 1996). However, contrary to the UADT cancers, rates of liver cancer have been increasing during the past 20 years. This is likely a consequence of the increasing

prevalence of hepatitis B and C (Pöschl & Seitz, 2004). In the United States, there has been an increase in the rates of liver cancer for all race–sex groups since the time period 1981 through 1985, with blacks having higher rates than whites and males having higher rates than females (Fig. 4). For the most recent time period, the rate for black males was 11/100,000, whereas the rate for white females was 2.6/100,000. The pooled risks of liver cancer associated with daily intake of alcohol ranged from 1.17 (95% CI = 1.11-1.23) for 25 g to 1.36 (95% CI = 1.23-1.51) for 50 g to 1.86 (95% CI = 1.53-2.27) for 100 g (Bagnardi et al., 2001). However, the role of chronic hepatitis B virus and hepatitis C virus infection was not considered.

Recent epidemiologic evidence has linked intake of alcohol to cancers of the colorectum and female breast (Jensen et al., 1996). These cancers are common in developed countries. In the United States, breast cancer is the number one cancer among women, accounting for 32% of all cancers. The lifetime probability of developing breast cancer is 1/7 (American Cancer Society, Inc., Surveillance Research, 2004). Colorectal cancer is the number three cancer among both men and women, accounting for 11% of all cancers. The probability of developing colorectal cancer is 1/17 for men and 1/18 for women (American Cancer Society, Inc., Surveillance Research, 2004). Therefore, even modest increases in risk of these cancers can have important public health implications (Bagnardi et al., 2001).

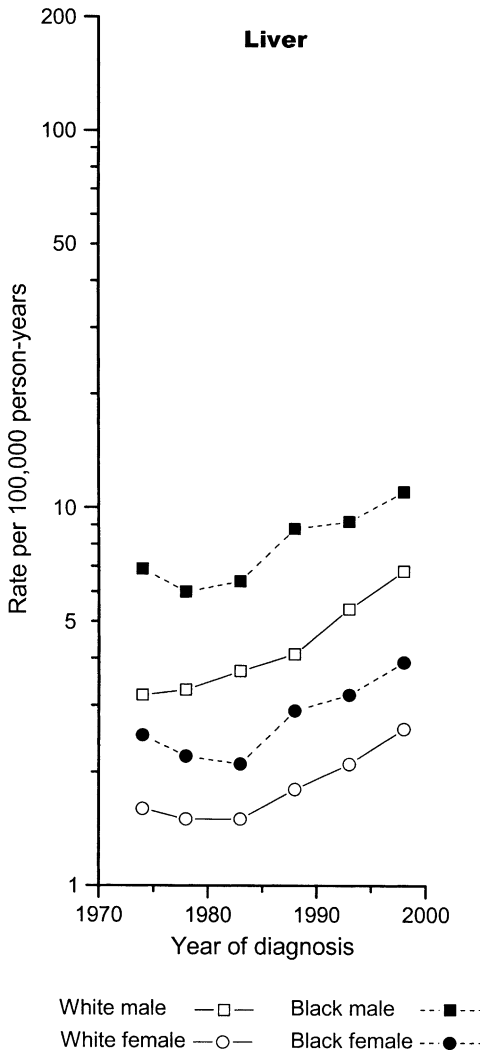

Fig. 4. Age-adjusted (2000 U.S. standard) incidence rates for liver cancer by race and sex, in nine SEER registries, 1973-2000. From Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence – SEER 9 Regs Public-Use, Nov 2003 Sub (1973-2001), National Canter Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2004, based on the November 2003 submission.

Rates for colorectal cancer are higher for males (range, 57/100,000–78/100,000) than for females (range, 47/100,000–57/100,000 (Fig. 5). There appears to be a slight decrease in incidence for whites and a slight increase for blacks, which resulted in a crossing over of the sex-specific rates in the 1980s. The pooled alcohol-associated risks for colorectal cancer are modest, ranging from 1.08 (95% CI = 1.06-1.10) for 25 g of alcohol consumed per day to 1.18 (95% CI = 1.14-1.22) for 50 g per day to 1.38 (95% CI = 1.29-1.49) for 100 g per day (Bagnardi et al., 2001). Although beer consumption was most strongly linked to cancer of the rectum in early studies (Jensen et al., 1996), the meta-analysis considered only total alcohol.

Breast cancer is the only alcohol-associated cancer for which rates for whites exceed those for blacks during the whole time period (Fig. 6). It is also the cancer among this group with the highest incidence rate, reaching 142/100,000 for white women and 121/100,000 for black women in the most recent time period. Results from the meta-analysis show a consistent pattern of increasing risk for breast cancer starting at about one to two drinks per day, with risk reaching 1.46 (95% CI = 1.33-1.61) for daily consumers of 58 g of alcohol or around five drinks per day in comparison with the risk for a woman who drank no alcohol (Collaborative Group on Hormonal Factors in Breast Cancer, 2002). It has been estimated that there is about a 10% increase in breast cancer risk for each 10 g of alcohol consumed (Collaborative Group on Hormonal Factors in Breast Cancer, 2002).

Since the time period 1981 through 1985, rates for cancer of the pancreas for blacks of both sexes have exceeded rates for whites (Fig. 7). In the most recent time period, black men have the highest incidence rate, reaching 18.4/100,000, whereas white females have the lowest rate, 9.5/100,000. Only white males show a consistent pattern, with rates decreasing from 15.1/100,000 in the time period 1973 through 1975 to 12.5/100,000 in 1996 through 2000. Results of most epidemiologic studies have revealed little or no support for a causal relation between light and moderate alcohol use and risk of pancreatic cancer (Jensen et al., 1996). However, heavy alcohol consumption may be related to risk of pancreatic cancer (Silverman et al., 1995). In the meta-analysis, the pooled risk for cancer of the

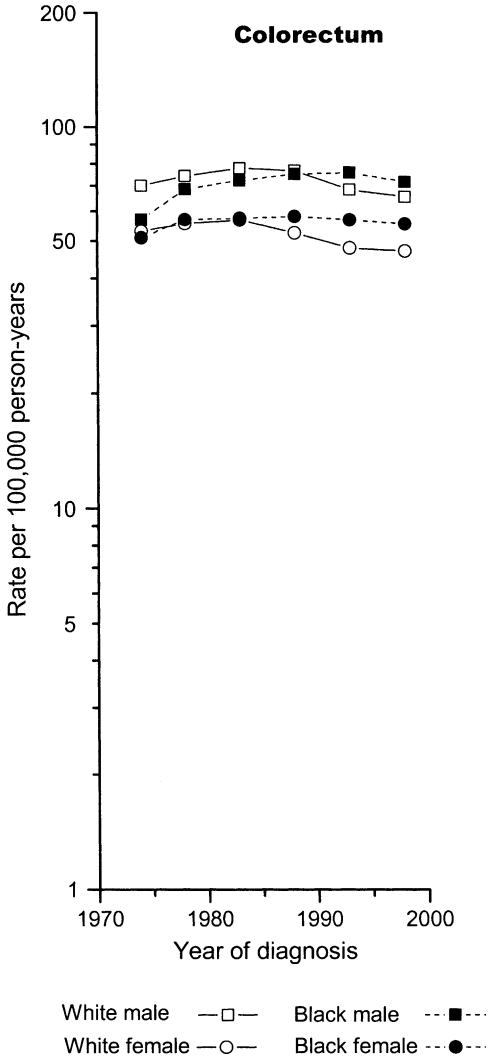

Fig. 5. Age-adjusted (2000 U.S. standard) incidence rates for colorectal cancer by race and sex, in nine SEER registries, 1973-2000. From Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence – SEER 9 Regs Public-Use, Nov 2003 Sub (1973-2001), National Canter Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2004, based on the November 2003 submission.

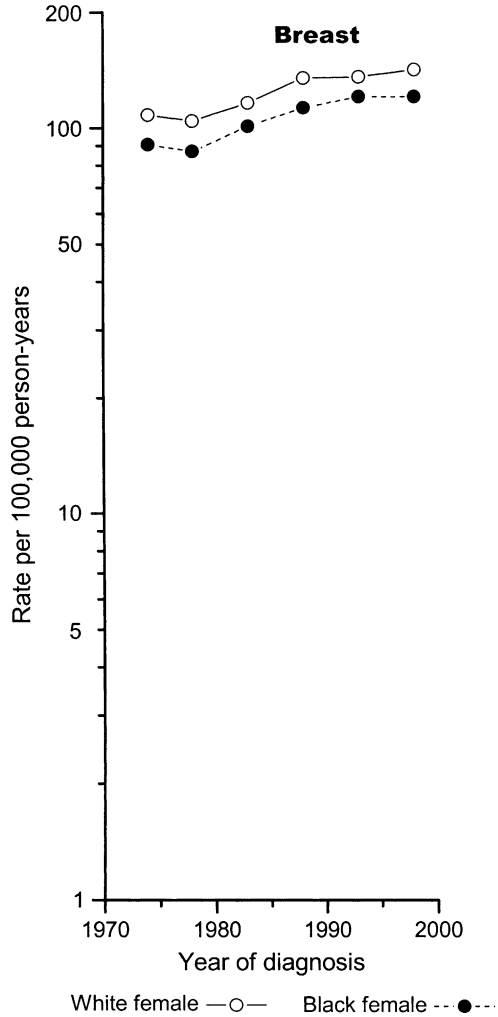

Fig. 6. Age-adjusted (2000 U.S. standard) incidence rates for female breast cancer by race, in nine SEER registries, 1973-2000. From Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence – SEER 9 Regs Public-Use, Nov 2003 Sub (1973-2001), National Canter Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2004, based on the November 2003 submission.

pancreas was small, ranging from 0.98 (95% CI = 0.90-1.05) to 1.05 (95% CI = 0.93-1.18) to 1.18 (95% CI = 0.94-1.49) for intake of 25 g, 50 g, and 100 g of alcohol per day, respectively (Bagnardi et al., 2001).

The NCI studied cancer of the pancreas in Detroit, Atlanta, and New Jersey to investigate reasons for the high rates of this cancer among blacks in comparison with whites. Subjects included both males and females, with 486 cases (307 white, 179 black) and 2,109 control subjects (1,164 white, 945 black). In this study, ORs of 2.0 or higher were observed for black men who drank 57 or more drinks per week (OR = 2.2, 95% CI = 0.9-5.6) and for black women who drank 21 or more drinks per week (OR = 2.5, 95% CI = 1.0-5.9). Smaller risks were observed for white men who drank 57 or more drinks per week (OR = 1.4, 95% CI = 0.6-3.2). There was no excess risk for white women who drank. These racial variations, if real, may be due to differences in drinking habits or in susceptibility to alcohol-induced pancreatic cancer (or to both) (Silverman et al., 1995).

4. Discussion and future directions

Although rates of smoking and drinking are declining, they remain the major risk factors for cancers of the oral cavity and pharynx and of the larynx, as well as for squamous cell esophageal cancer. Chronic alcohol use contributes to the risk of liver cancer, and moderate levels of alcohol use are associated with modest increases in the rates of cancers of the colorectum and breast. Heavy intake of alcoholic beverages may be related to a modest increase in pancreas cancer risk.

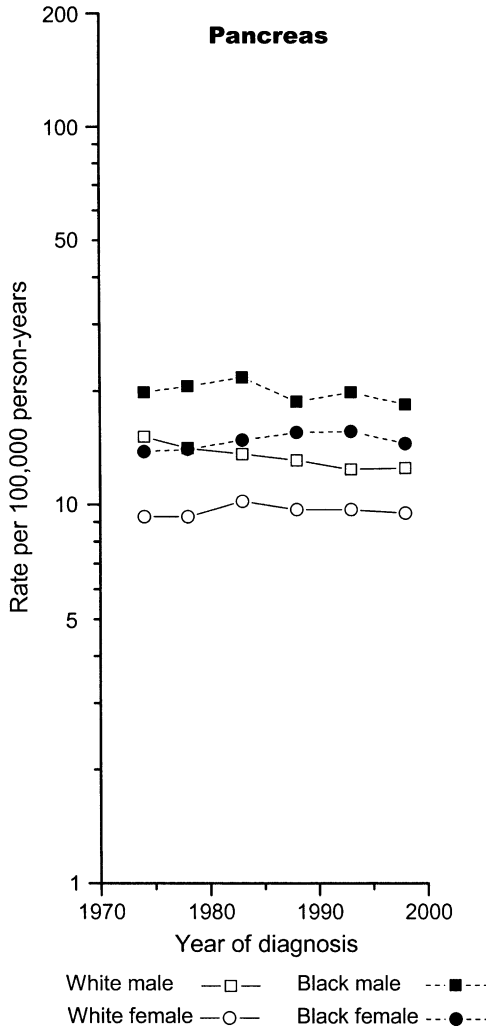

Fig. 7. Age-adjusted (2000 U.S. standard) incidence rates for pancreatic cancer by race and sex, in nine SEER registries, 1973-2000. From Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence – SEER 9 Regs Public-Use, Nov 2003 Sub (1973-2001), National Canter Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2004, based on the November 2003 submission.

Future directions related to alcohol-associated carcinogenesis include the following:

- Improve methodology by using uniform methods to report alcohol intake and uniform measures for analysis.
- Conduct studies aimed at quantifying the dose-response curve, especially at low levels of intake, and assessing, in detail, the role of type and concentration of alcoholic beverage consumed.
- Investigate alcohol-associated cancer risks in little-studied U.S. minority populations, such as Asian Americans, Hispanics and Latinos, and American Indians and Alaskan Natives.
- Enhance experimental work to better understand underlying mechanisms through which alcohol promotes carcinogenesis, including the role of co-factors and genetic polymorphisms of metabolism, and develop preventive strategies aimed at these mechanisms.

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